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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/214,251	03/10/99	KING	D CARP-0067

HM22/0720

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EXAMINER	
HELMS,L	
ART UNIT	**PAPER NUMBER**
1642	9

DATE MAILED: 07/20/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/214,251	King et al
Examiner	**Group Art Unit**
Larry R. H Ims Ph.D.	1642

☒ Responsive to communication(s) filed on *19 May 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1, 5, and 9-11* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 5, and 9-11* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *8*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Claims 2-4 and 6-8 have been canceled.

Claims 1, 5, 9, and 10 have been amended.

Claim 11 has been added.

Claims 1, 5, and 9-11 are under examination.

2. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

3. The following office action contains some NEW GROUNDS of rejections necessitated by amendment.

Rejections withdrawn

4. The rejection of claims under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendments to the claims.

5. The rejection of claim 10 under 35 U.S.C. 112, first paragraph is withdrawn in view of the amendment to the claim.

6. The rejection of claim 5 under 35 U.S.C. 102(b) as being anticipated by Pedley et al (Br. J. Cancer, Vol. 70, pp 1126-30, 1994) is withdrawn in view of the amendment to the claim.

Response to Arguments

7. The rejection of claims 1, and 9-10 and newly added claim 11 under 35 U.S.C. 102(b) as being anticipated by Pedley et al (Br. J. Cancer, Vol. 70, pp 1126-30, 1994) is maintained and made again.

a. The claims are drawn to a polymer- modified monovalent antibody fragment comprising an antigen binding fragment and at least one polymer molecule covalently linked in that each cysteine residue located outside the variable domain is either linked through its sulphur atom to the polymer or is disulfide linked with a second cysteine residue located in the antigen binding fragment wherein the antigen binding fragment is covalently linked to one, two, or three polymer molecules through one, two, or three cysteine residues. Further embodiments, wherein the polymer is an optionally substituted, straight or branch chain of poly(ethylene glycol), poly(propylene glycol), or poly(vinyl alcohol) and derivatives thereof, where the antibody is a Fab or Fab', wherein the antibody fragment is covalently attached to one or more effector or reporter molecules, and a composition of the antibody fragment with a pharmaceutically acceptable carrier.

b. The response of May 19, 2000 set forth on pages 8-9 has been carefully considered but has been deemed to be not persuasive. The response states that "Pedley therefore teaches the random attachment of PEG to residues other than cysteine, anywhere in the antibody" and "the Examiner is mistaken and Pedley does not teach the selective modification of cysteine residues with PEG." Further the response states "the present invention is therefore distinct from the disclosure of the Pedley reference in that the present invention utilizes (1) site specific

modification of (2) cysteines (3) in the nonvariable region of the antigen binding fragment while Pedley teaches (1) random modification of (2) amine groups (3) throughout the antibody fragment." In response to applicant's arguments, the reference of Pedly et al does teach site specific modification of cysteine residues and these residues can be outside the antibody variable domain (see page 1127 left column). In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., "antigen-binding fragments of the invention in which PEG has been specifically bonded to cysteine residues are disclosed in the present application as retaining more immunoreactivity than randomly PEG-modified Fab' fragments" and "the in vivo clearance of the specifically PEG-modified Fab' fragments of the invention was slower than that of randomly PEG-modified Fab' fragments") are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. In re Van Guens, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). In addition, claim 1 recites that the cysteine residue located outside the variable domain does not need to be modified, it can be in a disulfide linkage with a second cysteine residue in the antigen binding fragment. Thus, any cysteine residue, even those not found naturally in the antibody but produced by chemical modification that are outside the variable domain, as in the method of Pedly et al, can be modified and thus meet the limitation recited in the claim.

8. The following office action contains some NEW GROUNDS of rejections necessitated by amendment.

Claim Objections

9. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claim 10 has been renumbered as claim 11.

10. Claim 1 contains a typographical error in the term "compromising" in line 2.

11. Claim 1 contains a duplication of the term "poly (ethylene glycol)".

Claim Rejections - 35 USC § 112

12. Claims 1, 5, 9-10, and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1, 9-10, and 11 are indefinite for reciting "derivatives thereof" in claim 1. The claims are indefinite for reciting "derivative" as the exact meaning of the word is not known. The term "derivative" is not one which has a universally accepted meaning in the art nor is it one which has been adequately defined in the specification. The primary deficiency in the use of this

phrase is the absence of a ascertainable meaning for said phrase. Since it is unclear how the molecules are to be derivatized to yield the class of derivatives referred to in the claims, there is no way for a person of skill in the art to ascribe a discrete and identifiable class of compounds to said phrase.

b. Claims 1, 5, 9-10 and 11 are indefinite for reciting "optionally" in claim 1 for it is not clear what is meant by the term. What options are encompassed by the term?

c. Claim 1 is indefinite as being structured as an improper Markush claim. (See MPEP 2173.05(h)). It is not clear if the phrase "optionally substituted" is intended to modify the term straight, or branched chain polymer or poly(ethylene glycol), etc. Proper Markush claims are in the format of "X is selected from a group consisting of A, B, C, and D," or "the X is A, B, C or D".

Claim Rejections - 35 USC § 102

13. Claims 1 and 9-11 are rejected under 35 U.S.C. 102(e) as being anticipated by Griffiths et al (U.S. Patent 5,670,132, filed 9/20/94) .

a. The claims have been described supra.

b. Griffiths et al teach site specific attachment of PEG to thiols in an antigen binding fragment outside the variable region (see column 3 and 4) and the antigen binding fragment is a Fab or Fab' (see column 2, lines 46-58) and the antibody fragment has an effector attached (see abstract) and compositions comprising such.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 1, 5, and 9-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pedly et al (Br. J. of Cancer, Vol. 70, pp 1126-30, 1994) and further in view of Goodson et al

(Bio/Technology 8:343-346, 1990, IDS # 8) or Woghiren et al (Bioconjugate Chem. 4:314-318, 1993).

a. The claim recites an antibody fragment according to claim 1 wherein the polymer is methoxy(polyethylene glycol).

b. Pedley et al teach the covalent attachment of poly(ethylene glycol) (PEG) to an antibody, a Fab fragment, and a Fab' fragment of anti-CEA (see abstract). Pedley et al modified the cysteine residues outside the variable region of the antibody fragments with PEG producing two polymer molecules per antibody (see page 1128, right side first paragraph). Pedley et al also teach the radiolabelling of the PEG-modified antibodies (see page 1127, left column, Radiolabelling) and the PEG-modified antibody fragment in PBS (see page 1127 left column first full paragraph). Pedley et al does not teach the methoxy(polyethylene glycol). This deficiency is made up for in the teachings of Goodson et al or Woghiren et al.

c. Goodson et al and Woghiren et al teach a protein modified with the addition of methoxy(polyethylene glycol) to cysteine residues in the protein (see abstract).

d. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the methoxy(polyethylene glycol) of Goodson et al or Woghiren et al in the method of Pedley et al to produce a polymer-modified antigen binding fragment.

e. One of ordinary skill in the art would have been motivated to used the methoxy(polyethylene glycol) of Goodson et al or Woghiren et al in the method of Pedley et al to

produce a polymer-modified antigen binding fragment because Goodson et al teach "This method has general applicability for modifying any therapeutic protein at a specific site and thereby altering its potency" (see abstract). In addition, one of ordinary skill in the art would have been motivated to used the methoxy(polyethylene glycol) of Goodson et al or Woghiren et al in the method of Pedley et al to produce a polymer-modified antigen binding fragment because Woghiren et al teach "we have prepared a new activated form of PEG that is a stable reagent, but readily reacts with the thiol group of cysteine to form a disulfide-linked PEG aduct." (See introduction). In addition, one of ordinary skill in the art would conclude that many chemically altered PEG molecules could be used t produce a polymer-modified antigen binding fragment.

f. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

17. Claims 1, 5, and 9-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Griffiths et al (U. S. Patent 5,670,132) and further in view of Goodson et al (Bio/Technology 8:343-346, 1990, IDS # 8) or Woghiren et al (Bioconjugate Chem. 4:314-318, 1993).

a. The claim has been described supra.

b. Griffiths et al has been described supra. Griffiths et al does not teach the methoxy(polyethylene glycol). This deficiency is made up for in the teachings of Goodson et al or Woghiren et al.

c. Goodson et al and Woghiren et al have been described supra.

d. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the methoxy(polyethylene glycol) of Goodson et al or Woghiren et al in the method of Griffiths et al to produce a polymer-modified antigen binding fragment.

e. One of ordinary skill in the art would have been motivated to used the methoxy(polyethylene glycol) of Goodson et al or Woghiren et al in the method of Griffiths et al to produce a polymer-modified antigen binding fragment because Goodson et al teach "This method has general applicability for modifying any therapeutic protein at a specific site and thereby altering its potency" (see abstract). In addition, one of ordinary skill in the art would have been motivated to used the methoxy(polyethylene glycol) of Goodson et al or Woghiren et al in the method of Griffiths et al to produce a polymer-modified antigen binding fragment because Woghiren et al teach "we have prepared a new activated form of PEG that is a stable reagent, but readily reacts with the thiol group of cysteine to form a disulfide-linked PEG aduct." (See introduction). In addition, one of ordinary skill in the art would conclude that many chemically altered PEG molecules could be used t produce a polymer-modified antigen binding fragment.

f. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusions

18. No claims are allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

20. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

Sheela J. Huff

SHEELA HUFI
PRIMARY EXAMINER